PATENT
183/272

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	>	
	>	
GARTH J.S. COOPER	>	Group: 186
	>	Art Unit: 180
Serial No.: 236,985	>	
	>	Examiner: Lester L. Lee
Filed: August 26, 1988	>	
	>	
For: TREATMENT OF DIABETES MELLITUS	>	
	>	

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents
and Trademarks,
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.99, Applicant hereby makes the following documents of record in the above-identified application. The submission of the following information is not intended, nor should it be construed, to constitute an admission that any patent, article or other information referred to herein is "prior art" unless expressly designated as such. In accordance with 37 C.F.R. § 1.97(b), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no material information may exist. Neither should its submission be construed to indicate that a thorough search should not be conducted by the Examiner.

Copies of the following documents, which are listed on the accompanying form PTO-1449 (submitted in duplicate), are enclosed herewith. It is respectfully requested that these documents be: (1) fully considered by the Patent and Trademark Office during the examination of the application; and (2) printed on any patent which may issue in this application. Applicant

respectfully requests that a copy of form PTO-1449, as considered and initiated by the Examiner, be returned with the next communication.

DISCUSSION OF THE DOCUMENTS

A. CGRP

1. The following references relate to the isolation, characterization, and amino acid sequences of human and animal Calcitonin Gene Related Peptides (CGRPs) from a variety of tissues:

Foord, et al. Eur. J. Biochem. 170(1-2):373-80(1987) (AR);

Sewell et al., Soc. Neurosci. Abs. 13(1):42(1987) (AS);

Kimura et al., Neuropeptides 9(1):75-82(1987) (AT)

Minvielle et al., FEBS Lett. 203(1):7-10(1986) (AU); and

Morris et al., Nature 308:746-8(1984) (AV)

2. Craig et al., Biochem. Soc. Synp. 52:91-105(1986) (AW), reviews the expression and function of the human calcitonin/α-CGRP gene in health and disease.

3. Documents (AX)-(AZ) relate to the pharmacologic effects of CGRP. Tippins et al., J. Hypertens. 4(5):5102-5(1986) (AX) and Biochem. Biophys. Res. Commun. 134(3):1306-11(1986) (AY), and Holman et al., Peptides 7(2):231-5(1986) (AZ), discuss the vasodilator effects of human and cat CGRP.

4. Lenz et al., Gut. 26(6):550-5(1985) (BR), notes the effects of CGRP as an inhibitor of the increased secretion of gastric acid brought about by pentagastrin, histamine and bethanecol. Kimura (AT), supra, reported that porcine CGRP enhanced rat heart rate and was a heart muscle relaxant.

5. Craig, GB 2,141,430, December 19, 1984 (AL), relates to the synthesis by chemical and recombinant means of human CGRP

for use as an anti-hypertensive agent. Also noted are reagents for an immunoassay of the peptide and a DNA probe for use in a hybridization assay for the CGRP gene.

6. MacIntyre, WO8501658, April 25, 1985 (AM), relates to a human CGRP sequence and pharmaceutical compositions said to be useful for treating cardiovascular disease.

7. Evans et al., U.S. 4,530,839, July 23, 1985 (AA), and U.S. 4,736,023, April 5, 1988 (AB), relate to the synthesis of CGRP(s) by chemical and recombinant DNA techniques, and of analogues containing glutamic acid (natural) or lysine (analogue) at position 35. These molecules are said to be anti-hypertensive, anti-gastric acid secretion, regulators of calcium homeostasis, regulators of the secretion of hormones, and regulators of mood, appetite and behavior. Also set forth is a DNA sequence said to encode human CGRP.

8. Azria et al., EP 156,772, October 2, 1985 (AN), is said to relate to the synergistic effects of CGRP and analogues with calmodulin in the regulation of calcium metabolism in various bone diseases.

9. Janz et al, EP 188,400, July 23, 1986 (AO) and U.S. 4,720,483, January 19, 1988 (AC), relate to analogues of the 37-amino acid CGRP (amidated terminal COOH group and/or acylated terminal amino group) that are said to have vasodilatory, hypotensive, gastric acid secretion inhibiting, central nervous system and hypocalcemic activities. Also noted are DNA sequences said to code for the peptide and genetically-engineered microorganisms that express CGRP.

10. Kempe, U.S. 4,687,839, August 18, 1987 (AD), and U.S. 4,697,002, September 29, 1987 (AE), relate to the synthesis of human CGRP analogues wherein positions 36 and 37 of the peptide

chain are either the unnatural amino acids, D-serine, D-threonine, D-aspartic acid or D-asparagine, or the corresponding natural L-amino acids. The complete amino acid sequence of human CGRP is reported to be set forth.

11. Morita et al., EP 270,376, June 8, 1988 (AP), relates to derivatives of chicken CGRP said to be useful in treating calcium disorders, cardiac disease, ulcer disease, and brain circulatory disease. The CGRP derivatives comprise molecules in which various substitutions were made for the sulfur atoms in the disulfide bridge and for the aspartate at position 3.

B. "IAPP"

12. Westermark et al., Biochem. Biophys. Res. Commun. 140:827-31(1986) (BS), cited in the specification of the subject application, relates to the presence in the endocrine pancreas of an amyloid fibril protein related to CGRP, said peptide being homologous with the N-terminal sequence of the insulinoma (or islet) amyloid polypeptide (IAPP).

13. By immunochemical techniques employing antisera to a synthetic IAPP fragment and to insulin, Westermark et al., Diabetologia 30:887-92(1987) (BT), asserted IAPP immunoreactivity in both normal and diabetic human and animal β-islet cells of the pancreas.

14. Westermark et al., Proc. Nat'l. Acad. Sci. (U.S.A.) 84:3881-5 (1987) (BU), states that amyloid fibrils in human insulinoma and in islets of the diabetic cat are derived from a protein (termed "IAPP") also found in normal islets. Although the authors were only able to partially characterize the molecule, human "IAPP", like CGRP, was said to contain 37 amino acids. It was also reported to have a mass of 3850 daltons, and to have a 40% sequence homology with human CGRP.

15. Westermark et al., Am. J. Pathol. 127:414-7(1987) (BV) states that the islet amyloid in Type 2 diabetes mellitus and in diabetic cats contain a novel peptide similar to "IAPP", as determined by N-terminal sequencing. The cat peptide differed from the human peptide in 2 of the elucidated 16 amino acids.

16. Westermark et al., EP 263,802, April 13, 1988 (AQ), claims a kit containing "IAPP" and/or an anti-"IAPP" antibody preparation for immunoassays for IAPP. The IAPP preparation, which is claimed to consist of depolymerized islet amyloid, is said to be suitable for assays.

C. Amylin

17. Applicant (Cooper et al., Proc. Nat'l Acad. Sci. (U.S.A.) 84:8628-32(1987) (BW) and Lancet 2:966(1987) (BX)) disclosed the purification and characterization of a peptide from the amyloid-rich pancreas of patients with Type 2 diabetes mellitus. This peptide, which is referred to as Diabetes Associated Peptide (DAP) or amylin, was purified to homogeneity, and disclosed to have a mass of 3902 daltons and to contain 37 amino acids with a 46% sequence homology to CGRP. A 16-amino acid segment of amylin contained conserved sequences of the insulin A chain. Applicants proposed amylin (or DAP) to be pathogenic in Type 2 Diabetes Mellitus.

REMARKS

This application was filed in the U.S. on August 26, 1988, having a U.K. priority date of August 26, 1987. None of the above references disclose or suggest the inventions described and claimed in this application, including the use of amylin, deamidated amylin and CGRP in the treatment of Type 1 diabetes and hypoglycemia.

It is especially noteworthy that while the Westermark and Johnson patent application (AQ), first published on April 13, 1988, almost eight months after applicant's priority date, hypothesizes that Type 1 diabetes may involve IAPP deficiency, they do not suggest or claim its use in the treatment of Type 1 diabetes. They state only that IAPP "might perhaps" be useful in "IAPP deficiency cases" (page 6, lines 45-50).

Of course, even in an "IAPP deficiency case," one could not envision injecting a substitute peptide into humans that was incomplete or of the incorrect sequence. The Westermark and Johnson application (AQ) specifically states that the sequence they assigned for "IAPP" in their priority document was both wrong and incomplete (p. 8, lines 48-50), and that the sequence shown in their application (AQ) was still incomplete on international filing (p. 8, line 34).

Additionally, and in any event, one could not envision introducing into humans a molecule which had no known activity and whose biologic effect, therefore, could not be monitored and evaluated. In this regard, the Westermark and Johnson application (AQ) further specifically states that the activity of the so-called IAPP molecule was completely unknown (p. 6, line 43). Thus, the (AQ) document does not, of course, define the structural modifications of amylin necessary for full biologic activity (i.e., Cys^2-Cys^7 disulfide and C-terminal amidation), which were discovered by applicant and are set forth in the instant application. See also Cooper et al. (BW), Cooper et al. (BX), and U.S. Serial No. 275,475 infra.

Applicant also wishes to inform the Examiner of applications related to the above-captioned case: (1) Cooper, "Peptides," U.S. Serial No. 346,624, filed May 1, 1989 (first filed

in the U.K. on April 27, 1987), and (2) Cooper and Greene, "Treatment of Type 2 Diabetes Mellitus," U.S. Serial No. 275,475, filed November 23, 1988 (first filed in the U.S. on January 11, 1988). The first case relates to amylin and the second to the treatment of "Type 2" or "non-insulin dependent" diabetes mellitus.

Respectfully submitted

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Date: 11/10/89

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